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ORIGINAL ARTICLE

Assessment of Local Tissue Responses to Subcutaneous Implantation of Polyetheretherketone and Polymethyl Methacrylate-Based Materials

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Abstract

Background/Aim: In surgical dentistry, maxillofacial surgery and traumatology, bone tissue regeneration is one of the most pressing challenges. Aim of this study was assessment of local irritant effects following subcutaneous implantation of polyetheretherketone (PEEK) and polymethyl methacrylate (PMMA)-based devices, with determination of their biocompatibility and safety for intended applications in dental practice.

Methods: The study used 30 male Wistar rats (200 g ± 10 g, 9–10 weeks old) to evaluate inflammatory responses to four subcutaneous implants (PEEK, 3DF, Apium, Bonlecule) over 7, 30 and 60 days. Histological analysis assessed cell infiltration, necrosis, neovascularisation, fibrosis and capsule formation using standardised scoring systems. Statistical comparisons were made via one-way ANOVA ($p < 0.05$) to analyse intergroup differences in tissue reactions.

Results: Macroscopic examination showed stable implant integration with no structural changes, while microscopic analysis revealed mild mononuclear infiltration and progressive fibrous tissue replacement, with the strongest response in the Bonlecule group at day 7 and the weakest in PEEK by day 60. Histopathology indicated vascular dilation, reduced fibroblasts and increased immune cells, but no necrosis or fatty infiltration, with PEEK exhibiting the thinnest proliferation zone by day 60. Morphometric data confirmed Bonlecule had the thickest proliferation zone (91.9 µm at day 7), while PEEK showed the most significant reduction (28.34 µm by day 60).

Conclusion: The study confirmed high biocompatibility of PEEK and PMMA implants, with PEEK showing optimal integration and minimal tissue reaction, making it suitable for dental applications. The 3DF implant demonstrated the lowest bioresorption, remaining structurally intact over the two-month observation period. These findings support the clinical use of these materials, particularly PEEK, which meets all biocompatibility requirements with moderate immune response and vascularisation.

Key words: Material testing, biocompatibility; Polyetheretherketone; Polymethyl methacrylate; Subcutaneous; Implants.

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Introduction

In surgical dentistry, maxillofacial surgery and traumatology, bone tissue regeneration is one of the most pressing challenges.[1] The development of new biocompatible materials that can be used to restore lost tissues and functions is crucial. The use of polymeric materials for implants and membranes has significantly expanded the possibilities for treating extensive bone defects.[2-5] One of the key tasks in this field is the development of implant materials that not only possess high mechanical strength and durability but also exhibit minimal reaction from surrounding tissues upon implantation. This is particularly important to ensure successful implant integration and prevent complications such as inflammation, fibrosis, or rejection.

According to the World Health Organization (WHO), oral diseases, including tooth loss, affect approximately 3.5 billion people worldwide, making them one of the most prevalent health issues.[6] However, the success of implantation largely depends on the biocompatibility of the materials used for implants. Research shows that about 10–15 % of post-implantation complications are associated with an adverse tissue reaction to foreign materials, highlighting the need for developing new, safer alternatives.[7]

Polyetheretherketone (PEEK) and polymethyl methacrylate (PMMA) are promising materials for use in dental practice due to their unique physical-mechanical properties, such as high strength, wear resistance and biocompatibility.[8] PEEK, a semi-crystalline thermoplastic, is known for its excellent mechanical properties, such as stiffness and resistance to thermal degradation, making it ideal for load-bearing dental implants.[9] Its biocompatibility, low inflammatory potential and ability to integrate with bone tissues have led to its widespread use in orthopaedic and dental implants.[10] PMMA, on the other hand, is a versatile thermoplastic polymer, widely used for provisional dental restorations and denture bases due to its ease of processing and relatively low cost.[11] Though its mechanical properties are not as robust as PEEK, PMMA exhibits good biocompatibility and has been extensively used in a variety of dental applications, including implants, due to its favourable physical properties and long-term stability.[12] However, despite their widespread application, issues related to local tissue reactions following subcutaneous implantation of these materials remain insufficiently studied. In particular, it is important to evaluate how different material compositions and structures affect inflammation, fibrosis, vascularisation and immune response in surrounding tissues. According to recent research, the material's structure and composition directly influence these processes, including the degree of inflammatory reaction, fibrous capsule formation and angiogenesis. For example, studies have shown that materials with high porosity and specific surface treatment help reduce inflammatory responses and enhance vascularisation, which is critical for successful implant integration.[13]

The development of new materials that not only meet biocompatibility requirements but also minimise the risks of post-implantation complications represents a crucial direction in modern dentistry. This is particularly relevant for patients with chronic diseases, immunodeficiencies, or increased sensitivity to foreign materials. Understanding the mechanisms of implant-tissue interactions will enable optimisation of their composition and structure to achieve better clinical outcomes. However, the severity and dynamics of inflammatory processes following implantation remain insufficiently studied, necessitating comprehensive investigation in this field.

Therefore, the present study aimed to solve an important problem in dentistry and maxillofacial surgery - creating biocompatible materials that promote successful tissue integration while minimising the risks of postoperative complications. Aim of the study was assessment of local irritant effects following subcutaneous implantation of PEEK and PMMA -based devices, with determination of their biocompatibility and safety for intended applications in dental practice.

Methods

Experimental animals

Male Wistar rats (n = 30; 200 g ± 10 g; age: 9 – 10 weeks) were used. Throughout the study duration, rats were individually housed in welfare-compliant stainless-steel cages (0.37 m^2

floor area, 50 cm height) designed to accommodate natural postures. All enclosures featured moisture-absorbing bedding (Delta Feeds, Moscow, Russia) to maintain hygiene and provide adequate cushioning.

All subjects underwent comprehensive health screening, including biochemical profiling and weight analysis. Animals failing to meet predefined physiological standards were excluded. Qualified subjects were then randomly allocated to experimental groups to ensure unbiased distribution and enhance statistical validity.

Experimental design

Experimental animals underwent subcutaneous implantation with subsequent evaluation of local inflammatory responses at designated time intervals. The animals were allocated into four experimental groups:

Group I (n = 5): Animals with PEEK implant;
Group II (n = 5): Animals with 3DF implant;
Group III (n = 5): Animals with Apium implant;
Group IV (n = 5): Animals with Bonlecule implant.

The implants were printed (*LLC "BonaByte"*, Moscow, Russia) on an *Apium P220* and *Apium M220 3D* printers from the following materials: PEEK – TECAFIL PEEK VX MT; 3DF – *Evonik Vestakeep i4g 3DF*; Apium – *Evonik Vestakeep i4g 3DF*; Bonlecule – *Bonlecule Ossfila* (Table 1). The implants had a diameter of 7-10 mm and a thickness of 1-2 mm.

Animals from all experimental groups (I – IV) underwent subcutaneous implantation of the materials in the area under the scapula (Figure 1) and were euthanised at predetermined time points (days 7, 30 and 60) via anaesthetic overdose using intramuscular ketamine (50 mg/kg) combined with intraperitoneal xylazine (5 mg/kg).

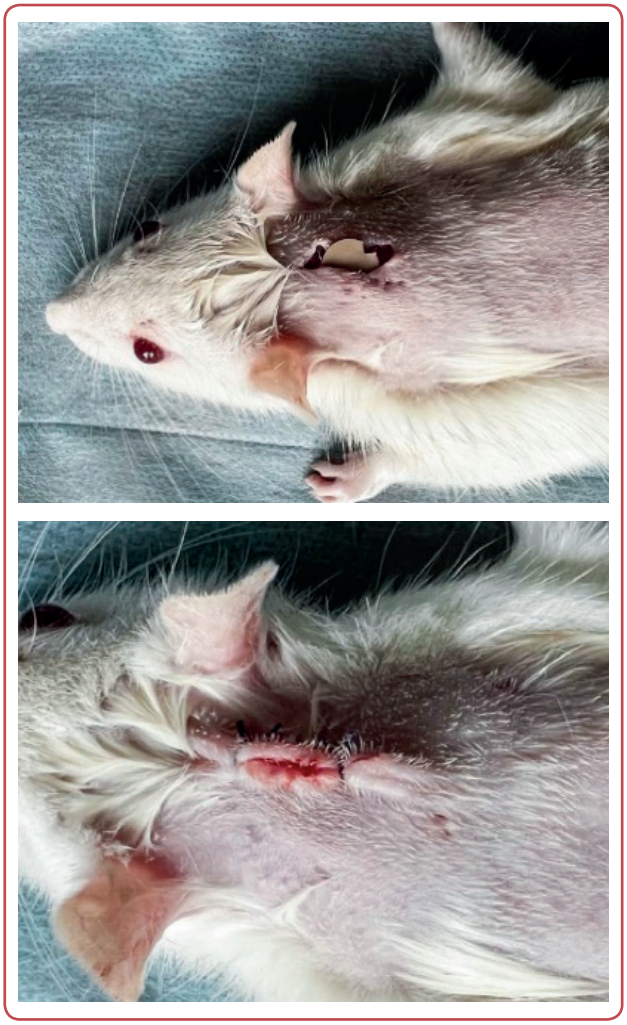


Figure 1: Subcutaneous implantation procedure in rats. (a) Rat with implanted disc (subcutaneous implantation under the scapula). (b) Surgical site after implantation, with sutured area.

Table 1: Description of implant materials

Implant type	Material	Material features	Printer
Polyetheretherketone (PEEK)	Tecafil PEEK VX MT	3D printer filaments based on PEEK, diameter 1.75 mm	Apium M220
3DF	Evonik Vestakeep i4g 3DF	3D printer filaments based on PEEK, diameter 1.75 mm	Apium M220
Apium	Evonik Vestakeep i4g 3DF	3D printer filaments based on PEEK, diameter 1.75 mm	Apium P220
Bonlecule	Bonlecule Ossfila	3D printer filaments based on composite of hydroxyapatite and PMMA, diameter 1.75 mm	Apium P220

Histological analysis

The excised specimens were fixed in 10 % neutral buffered formalin. At the Laboratory of Experimental Morphology and Digital Pathology, after examination of pre-fixed specimens on the histology cutting station (*LEEC* Ltd), histotopographic sectioning of the study samples/specimens was performed. The implant material resisted mechanical manipulation during histological sectioning due to its high density. The implant disc with adjacent local tissues was oriented transversely to ensure the specimen contained all required tissue layers for examination. Each histological cassette contained a single specimen.

Tissue samples placed in histology cassettes underwent post-fixation in appropriate fixatives for up to 48 hours, followed by standard histological processing using a *Leica TP1020* carousel tissue processor. Subsequently, samples were embedded in *Histomix* paraffin medium (*BioVitrum*) on a *HistoStar* embedding station (*Thermo Scientific*).

For morphological analysis, 3–5 µm sections were prepared using a *Leica RM2235* microtome and stained with haematoxylin and eosin (H&E; *BioVitrum*) and Masson's trichrome stain (*BioVitrum*). Histological specimens were examined using *Olympus CX41* and *Leica DM 2000* microscopes, with digital microphotography captured by a *Leica ICC50 HD* camera. Image processing and analysis, including morphometric studies, were performed using QuPath software (*Platrun LG* computer system) at five magnification levels: ×2.5, ×10, ×20, ×40 and ×100 (oil immersion). Morphometric analysis was conducted in 10 randomly selected microscopic fields at ×400 magnification.

A comprehensive microscopic evaluation of peri-implant tissue structures was performed at three-time intervals post-implantation: 7 days (Phase 1), 30 days (Phase 2) and 60 days (Phase 3) in laboratory rats. The presence and quantity of the aforementioned cell types (neutrophils, lymphocytes, macrophages, giant cells, plasma cells) were scored as follows:

1 = rare (1 – 5 cells per field of view);
2 = 5-10 cells per field of view;
3 = abundant infiltrate (> 10 cells per field of view);
4 = densely packed cells.

At each implantation timepoint, the extent of the cellular reaction was assessed relative to the implant volume (Table 2):

Table 2: Histological scoring system – cell type/tissue response

Cell type/the response	Score				
	0	1	2	3	4
Neutrophils	0	rare, 1 – 5[a]	5 – 10[a]	Abundant infiltrate	Densely packed cells
Lymphocytes	0	rare, 1 – 5[a]	5 – 10[a]	Abundant infiltrate	Densely packed cells
Plasma cells	0	rare, 1 – 5[a]	5 – 10[a]	Abundant infiltrate	Densely packed cells
Macrophages	0	rare, 1 – 5[a]	5 – 10[a]	Abundant infiltrate	Densely packed cells
Giant cells	0	rare, 1 – 2	3 – 5	Abundant infiltrate	Densely packed cells
Necrosis	0	Minimal	Light	Medium	Severe

[a] *Number of cells per field at ×400 magnification*

Table 3: Histological scoring system for tissue response

The response	Score				
	0	1	2	3	4
Neovascularisation	0	Minimal capillary proliferation, 1 – 3 foci of neovascularisation	Groups of 4 – 7 capillaries with fibroblastic structures	A wide band of capillaries with fibroblastic structures	An extensive band of capillaries with fibregular structures
Fibrosis	0	A narrow band of connective tissue (scar)	A moderately thick band of connective tissue (scar)	Thick band of connective tissue (scar)	Intense band of connective tissue (scar)
Fatty infiltration	0	Minimum amount of fat associated with fibrosis	Multiple layers of fat and fibrosis	Extensive and extensive accumulation of fat cells around the implant site	Extensive fat completely surrounding the implant

0 = absent;
1 = ≤ 1/4 of the implant volume;
2 = ≤ 1/2 of the implant volume;
3 = > 1/2 of the implant volume;
4 = > 3/4 of the implant volume.

The presence of necrosis and oedema was assessed using a binary index: 0 for absence and 1 for presence (Table 3). Neovascularisation was scored as follows: 0 points for absence; 1 point for minimal capillary proliferation with 1-3 neovascularisation foci; 2 points for groups of 4 – 7 capillaries with fibroblastic structures; 3 points for a wide band of capillaries with fibroblastic structures; and 4 points for an extensive band of capillaries with fibroblastic structures. Fibrosis was graded as: 0 points for absence; 1 point for a narrow band of connective tissue (scar); 2 points for a moderately thick band of connective tissue; 3 points for a thick band of connective tissue; and 4 points for an intensive band of connective tissue. Fatty infiltration was evaluated as: 0 points for absence; 1 point for minimal fat deposition with fibrosis; 2 points for several layers of fat and fibrosis; 3 points for extended and abundant accumulation of fat cells around the implantation site; and 4 points for extensive fat completely surrounding the implant. Capsule formation was scored as: 2 points for a well-defined capsule around the implant; 1 point for a mildly apparent capsule; and 0 points for absence of a capsule.

Statistical analysis

For normally distributed data, the group arithmetic mean (M) and standard deviation (SD) as measures of central tendency were calculated and sample variability using the data analysis toolkit in Microsoft Excel (version 14.0.4760.1000, 32-bit). Intergroup comparisons were performed using One-way ANOVA with statistical significance set at $p < 0.05$.

Results

Macroscopic description

Macroscopic examination of the implants and implantation sites at 7, 30 and 60 days revealed limited implant mobility with firm adherence to surrounding tissues, indicating successful integration and stable positioning. The implants maintained their original colour, demonstrating no structural or compositional changes. Their consistency was firm-yet-elastic, conforming to standard parameters for this material type and confirming functional suitability. Overall, the implants showed satisfactory condition with no visible signs of deformation or damage.

Microscopic description

In all four experimental groups (PEEK, 3DF, Apium, Bonlecule) across implantation periods, subcutaneous morphological evidence of implants was identified at the animal's withers projection. The observed characteristics varied by both timepoint and material composition. Histological sections revealed transverse orientation of implantation sites relative to surrounding tissues and skin.

The implantation site exhibited tubular and partially solid structures, with a stromal component consisting of proliferating loose and dense irregular fibrous connective tissues containing blood vessels. No replacement of the implant material was observed. The stroma displayed features of granulomatous inflammation – a foreign body reaction – that progressed from the periphery toward the centre, accompanied by gradually increasing vascularisation and diffuse replacement with fibrous tissue. Evaluation of the tissue response to subcutaneous implantation of PEEK and PMMA implants revealed mild focal mononuclear (lymphoid-histiocytic) infiltration adjacent to the implant materials (Table 4).

The highest mean tissue response score was observed in the "Bonlecule" group at day 7, measuring 1.46-fold greater than at day 60. The weakest day-7 response occurred in the "PEEK" group, showing 1.21-fold lower reactivity compared to "Bonlecule" group (Table 4, Figures 2, 3).

Thus, evaluation of peri-implant tissue responses to subcutaneous PEEK and PMMA implants revealed most pronounced histopathological changes in the "Bonlecule" group at day 7, while the "PEEK" group showed minimal alterations by day 60.

Histopathological examination of the peri-implant zone revealed pronounced vascular changes characterised by marked dilation and engorge-

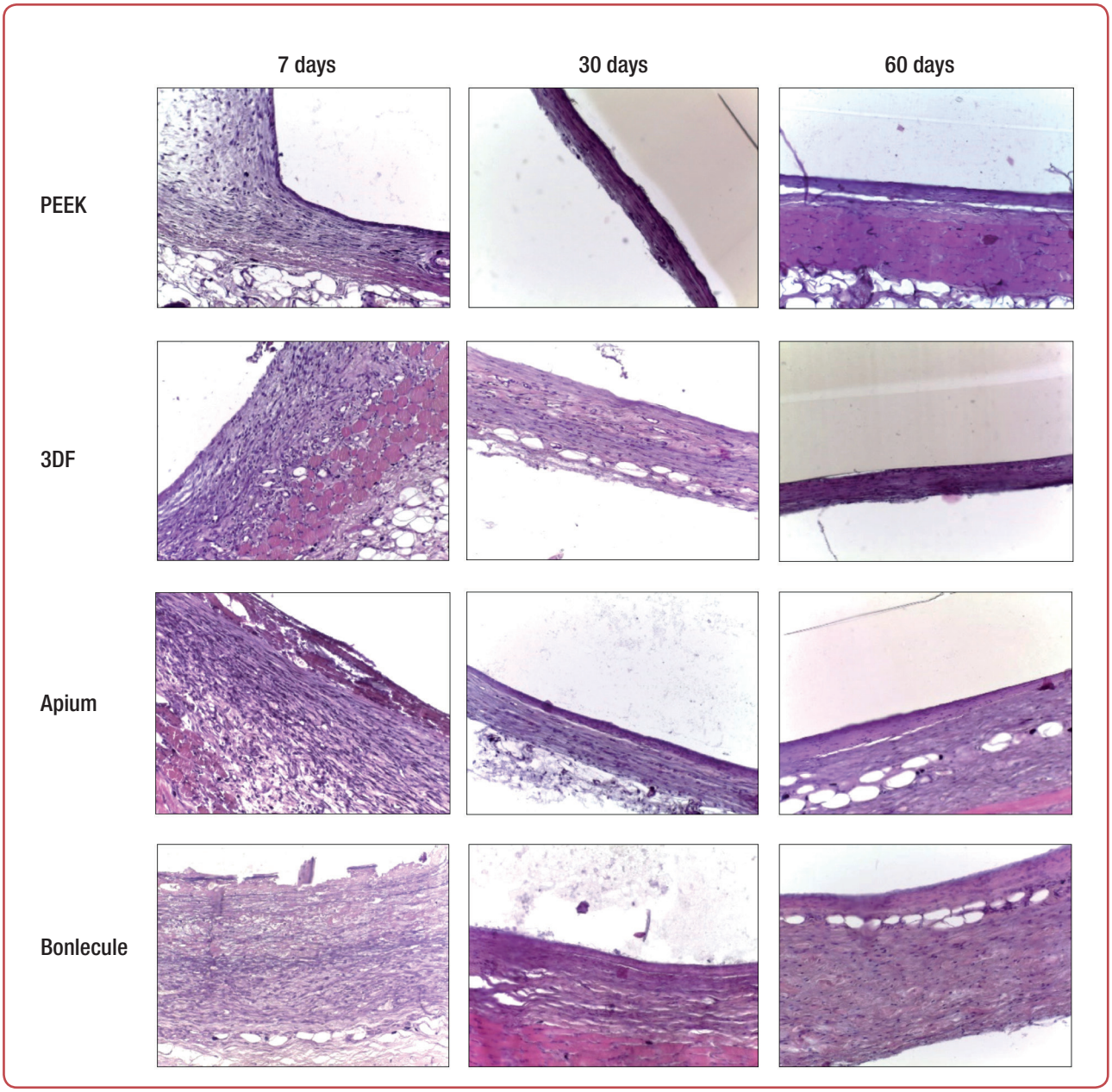


Figure 2: Morphological characteristics of the peri-implant tissue response following subcutaneous implantation of polyetheretherketone (PEEK) and polymethyl methacrylate (PMMA)-based implants. Staining: haematoxylin and eosin, magnification ×200.

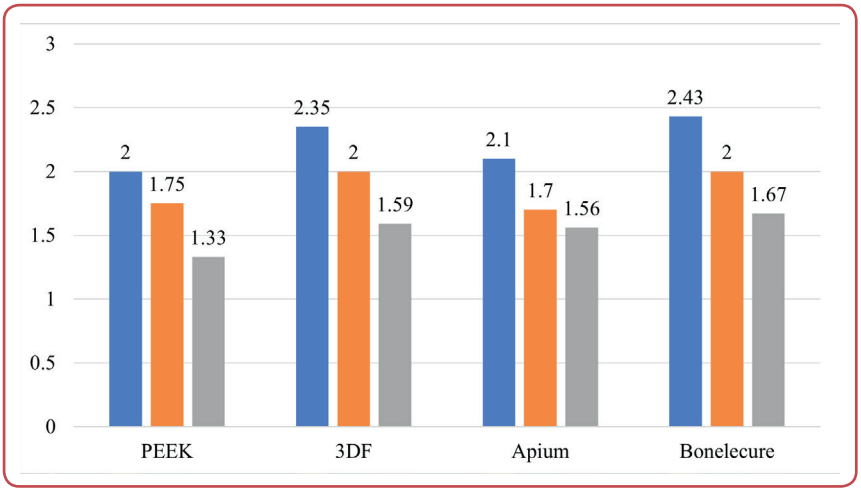


Figure 3: Mean tissue response scores of peri-implant tissues at different time points: blue column – day 7; orange – day 30; grey – day 60 ($p < 0.05$)

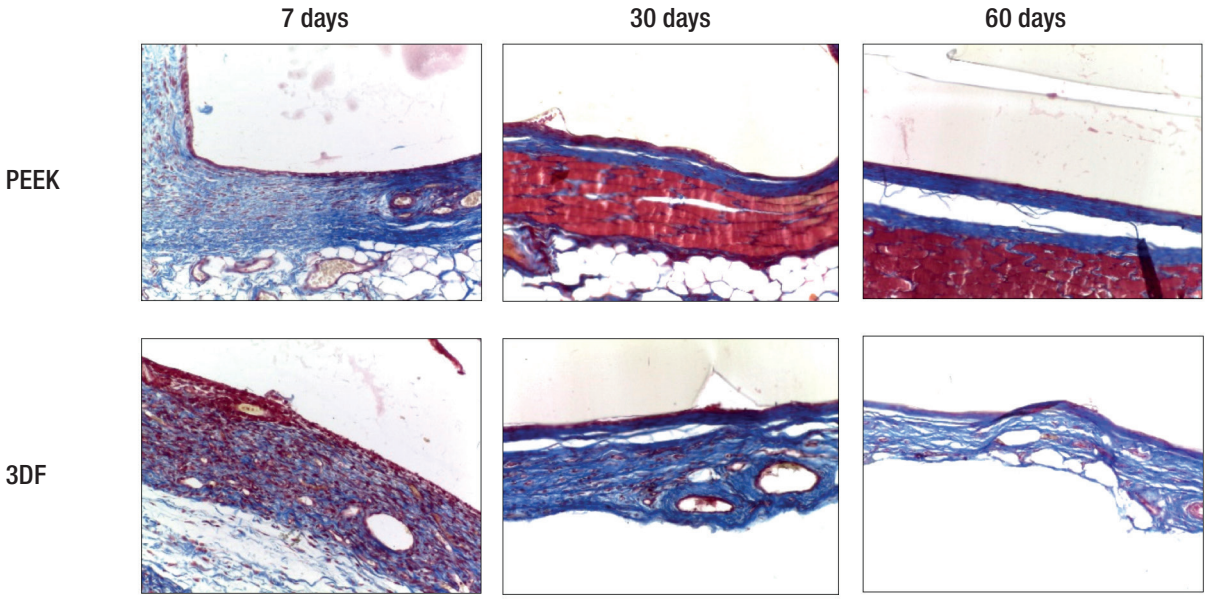
Table 4: Indicators characterising the response from the surrounding tissues during subcutaneous implantation of implants based on polyesteresterketone (PEEK) and polymethyl methacrylate (PMMA)

Group	Assessment after	Neutrophils	Lymphocytes	Macrophages	Giant cells	Necrosis	Neovascularisation	Fatty Infiltration	Average score for the response
PEEK	7 days	0	1.33	0	0	0	2.67	0	2.00
	30 days	0	0.83	0	0	0	2.67	0	1.75
	60 days	0	0.33	0	0	0	2.33	0	1.33
3DF	7 days	0	1.80	0	0	0	2.67	0	2.35
	30 days	0	1.33	0	0	0	2.67	0	2.00
	60 days	0	1.17	0	0	0	2.00	0	1.59
Apium	7 days	0	1.80	0	0	0	2.33	0	2.10
	30 days	0	1.67	0	0	0	1.80	0	1.70
	60 days	0	1.33	0	0	0	1.67	0	1.56
Bonlecule	7 days	0	2.53	0	0	0	2.33	0	2.43
	30 days	0	2.33	0	0	0	1.67	0	2.00
	60 days	0	2.00	0	0	0	1.33	0	1.67

ment of blood vessels. The fibrous connective tissue demonstrated a significant reduction in fibroblast population and fibroblastic lineage cells. Concurrently, a moderate increase in immune-competent cells was observed, including lymphocytes and macrophages (histiocytes). These findings suggest an active tissue remodelling process with distinct vascular and cellular responses to the implanted material.

Necrosis of the implantation bed and surrounding tissue, as well as the formation of a fatty infiltrate, was not observed in all the studied samples. In a comparative study of the implant bed in all experimental groups, the preservation of their area and volume was observed throughout all time points, no bioresorption was noted.

In the group of PEEK implants, the smallest thick-



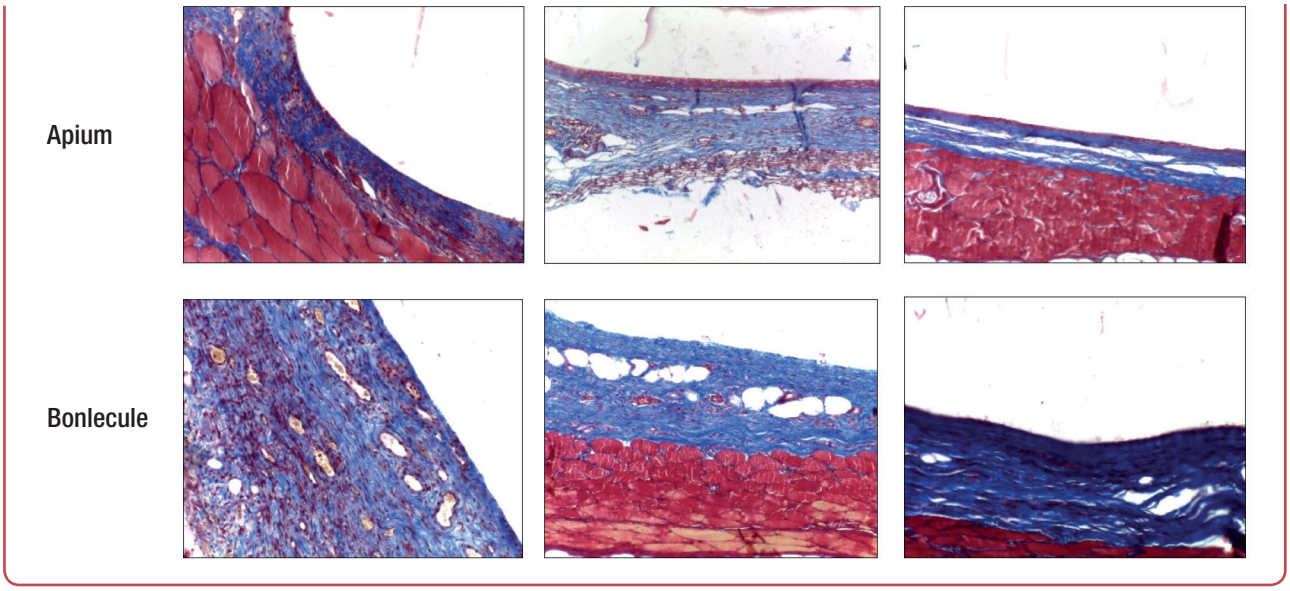


Figure 4: Histochemical characteristics of the implant proliferation zone during subcutaneous implantation of implants based on polyesteresterketone (PEEK) and polymethylmethacrylate (PMMA). Staining: Masson's trichrome magnification ×200.

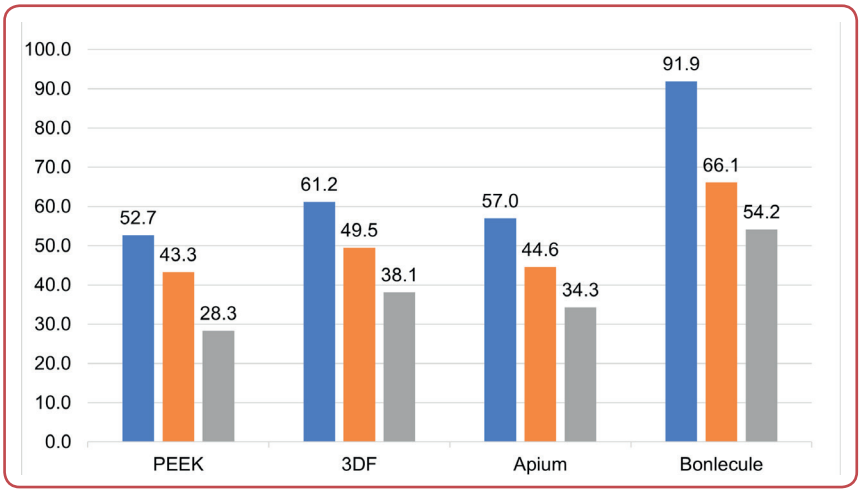


Figure 5: Thickness of the proliferation zone (in microns) of implants in different periods: blue column – 7 days; orange – 30 days; grey – 60 days ($p < 0.05$).

ness of the proliferation zone was observed on day 60, which is 1.86 times less than on day 7. The greatest thickness of the implant proliferation zone was observed in the Bonlecule group, by 1.74 times compared with the PEEK group on day 7 (Table 5, Figure 4, 5).

Table 5: Morphometric parameters characterising the thickness of the proliferation zone (microns) ($p < 0.05$)

Group	Thickness of the proliferation zone (microns)		
	7 days	30 days	60 days
PEEK	52.7	43.3	28.3
3DF	61.2	49.5	38.1
Apium	57.0	44.6	34.3
Bonlecule	91.9	66.1	54.2

Discussions

This study enabled comprehensive evaluation of tissue responses to subcutaneous implantation of PEEK and PMMA devices, assessing their biocompatibility and clinical applicability in dental practice. The results demonstrate that both materials exhibit high structural stability and minimal peri-implant tissue reactivity, confirming their suitability for clinical use.

The study revealed that both PEEK and PMMA implants induced only mild mononuclear inflammation (lymphocytic/macrophagic infiltration), indicative of favourable biocompatibility as supported by current research.[14] Maximum inflammatory response was observed in the "Bonlecule" group at 7 days, contrasting with the minimal reaction in "PEEK" at 60 days. These differences may be attributed to distinct material architectures and surface-tissue interactions.[15] The time-dependent decrease in inflammatory markers across all groups indicates gradual tissue adaptation and a reduction in immune response over time. Additionally, the biocompatibility of PEEK-based materials was thoroughly investigated, showing minimal tissue reaction and favourable integration with surrounding tissues.[16, 17]

The thickness of the proliferative zone formed around the implants varied depending on the material and observation period. At day 7, initial signs of the proliferative inflammatory phase were observed, characterised by the appearance of granulation tissue and active proliferation of microcirculatory vessels and fibroblasts.[18] By day 30, the thickness of the peri-implant zone significantly decreased due to the replacement of granulation tissue with loose fibrous connective tissue and reduced proliferative activity of vascular and fibroblastic components.[19] At day 60, the most pronounced compaction of collagen fibres was noted, resulting in thinning of the peri-implant zone. The smallest thickness of this zone was recorded in the "PEEK" group, suggesting a more favourable tissue response to PEEK compared to other materials.[20] Conversely, the greatest thickness of the proliferative zone was observed in the "Bonlecule" group, likely due to a more pronounced tissue reaction to this material. However, even in this group, the capsule thickness decreased over time, indicating gradual reduction of the inflammatory response and tissue adaptation.[21]

All experimental groups demonstrated moderate neovascularisation, indicating normal healing and implant integration processes. The fibrous tissue formation remained at moderate levels, further confirming the materials' good biocompatibility. The absence of necrosis and fatty infiltration in the peri-implant zone across all groups suggests minimal tissue damage and no significant complications.[22]

Histological analysis of highly porous samples revealed mild local foreign body reaction with phagocytosis of the implant material, signs of neovascularisation and partial focal replacement by fibrous tissue. These features persisted throughout the implantation period, indicating gradual material integration and tissue adaptation.[16] The adjacent tissues showed predominantly immune-competent cells, such as scattered lymphocytes, demonstrating minimal immune response and good biocompatibility.[23]

PEEK implants demonstrated the lowest inflammatory response and thinnest fibrous capsule formation, making them the preferred choice for dental applications. While PMMA implants initially provoked more pronounced tissue reactions, they nevertheless showed good integration and stability by day 60. These findings confirm that both materials can be successfully used in clinical practice, though PEEK may be particularly advantageous for patients with heightened sensitivity to foreign materials.[24]

The obtained data emphasise the importance of selecting an implantation material based on individual patient characteristics and clinical circumstances. For patients with chronic conditions or increased risk of inflammatory reactions, preference should be given to materials with minimal tissue response, such as PEEK. At the same time, PMMA may be used in cases requiring higher mechanical strength and load-bearing capacity. The results also highlight the potential of PEEK implants for use in osseointegration, which will be the subject of future studies.

Conclusion

The study results confirm that both PEEK- and PMMA-based implants exhibit high biocompatibility and can be successfully used in dental practice. The least bioresorbable was the 3DF implant, which remained intact in tissues throughout the entire observation period (2 months). Meanwhile, PEEK implants demonstrated moderate parameters characterising the response of immune-competent cells and degree of vascularisation in the implantation bed and surrounding tissues, meeting all biocompatibility requirements.

Thus, the studied implant samples with different physical-mechanical properties, proven biocompatibility and biosafety can be used for various clinical situations - particularly PEEK, which showed the best results in terms of integration and minimal tissue reaction.

Ethics

The Bioethics Commission of the Peoples' Friendship University of Russia named after Patrice Lumumba approved this study (Protocol No 64), dated 14 March 2023. All procedures were conducted in strict compliance with the ILAR guidelines for the care and use of laboratory animals, the "International recommendations for conducting biomedical research using animals" (EEC, Strasbourg, 1985) and the "European convention for the protection of vertebrate animals for experimental and other scientific purposes" (EEC, Strasbourg, 1986).

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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